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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/070,629	04/30/98	PALESE	P 6923-071-999

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EXAMINER	
SCHEINER, L	
ART UNIT	**PAPER NUMBER**
1648	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/070,629	Palese et al.
Examiner	**Group Art Unit**
Lauri Sch iner	1648

[X] Responsive to communication(s) filed on *Nov 24, 2000*

[ ] This action is **FINAL.**

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

[X] Claim(s) *1-5 and 20-29* is/are pending in the applicat

Of the above, claim(s) *23-27* is/are withdrawn from consideration

[ ] Claim(s) _____ is/are allowed.

[X] Claim(s) *1-5, 20-22, 28, and 29* is/are rejected.

[ ] Claim(s) _____ is/are objected to.

[ ] Claims _____ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.

[ ] The specification is objected to by the Examiner.

[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [X] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____ .

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachm nt(s)

[ ] Notice of References Cited, PTO-892

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). *15*

[ ] Interview Summary, PTO-413

[ ] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Claims 1-5 and 20-29 are pending in this application. Newly submitted claims 23-27 are drawn to an invention that is independent or distinct from the invention originally claimed since said claims specifically set forth that the respective heterologous regions encode **specific** tumor antigens such as MAGE-1, GAGE-2, MUC-1, etc., rather than the originally claimed heterologous regions which encode tumor associated antigens (TAA).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 23-27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 1-5, 20-22, 28 and 29 are considered below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 20-22, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen,* 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim,* 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). Claims 1-5, 20-22, 28 and 29 are drawn toward a recombinant influenza virus wherein a structural gene contains a heterologous region encoding a tumor-associated antigen. Additional limitations are provided concerning whether or not the virus is killed, live, or attenuated. A pharmaceutically acceptable carrier (vaccine) is also contemplated. Claims 1-5, 20-22, 28 and

29 are drawn toward a product consisting of a recombinant influenza virus containing any region encoding any tumor-associated antigen. The written description requirement under Section 112, first paragraph, sets forth that the claimed subject matter must be supported by an adequate written description that is sufficient to enable anyone skilled in the art to make and use the invention. The courts have concluded that the specification must demonstrate that the inventor(s) had possession of the claimed invention as of the filing date relied upon. Although the claimed subject matter need not be described identically, the disclosure relied upon must convey to those skilled in the art that applicants had invented the subject matter claimed. *In re Wilder, et al.*, 222 U.S.P.Q. 369 (C.A.F.C. 1984). *In re Werthheim, et al.*, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *In re Driscoll,* 195 U.S.P.Q. 434 (C.C.P.A. 1977). *Utter v. Hiraga,* 6 U.S.P.Q.2d 1709 (C.A.F.C. 1988). *University of California v. Eli Lilly,* 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997). *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 U.S.P.Q.2d 1016-1031 (C.A.F.C. 1991). *Fiers v. Sugano,* 25 U.S.P.Q.2d 1601-1607 (C.A.F.C. 1993). *In re Bell,* 26 U.S.P.Q.2d 1529-1532 (C.A.F.C. 1993). *In re Deuel,* 34 U.S.P.Q.2d 1210-1216 (C.A.F.C. 1995). The significance of conception and reduction to practice was further addressed by the court in *Fiers v. Sugano* where it was emphasized that "[c]onception is a question of law, reviewed *de novo* on appeal, and if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated; thus, regardless of complexity or simplicity of method of isolation employed, conception of DNA sequence, like conception of any chemical substance, requires definition of that substance other than by its functional utility." Thus, the courts have emphasized that the inventor must clearly and unambiguously identify the salient characteristics and properties of any given claimed

nucleotide sequence. It is not sufficient to provide a vague reference to the biological activity of any given nucleotide sequence or merely a generic method of obtaining it.

Applicants' disclosure fails to provide adequate written support for the invention as broadly claimed. That is, applicants' claims encompass regions encoding any tumor-associated antigen. However, the disclosure provides discussion of β-*gal* as the sole heterologous insert. As such, limiting the scope of the claims commensurate with that which has been described would be acceptable. Again, the disclosure fails to provide an adequate written description for subject matter encompassing other RNAs (or cDNAs) which would function similarly with respect to proper expression, immunogenicity, etc.

Claims 1-5, 20-22, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. As set forth above, claims 1-5, 20-22, 28 and 29 are drawn toward a recombinant influenza virus containing, within a structural gene, a region which encodes any tumor-associated antigen. Moreover, the recombinant may be admixed with a pharmaceutically acceptable carrier for use as vaccine. It is asserted that the claims as reasonably interpreted could encompass virtually any nucleotide sequence encoding virtually any tumor-associated antigen or epitope, none of which (with the possible exception of β-*gal*)are adequately supported by the disclosure. Applicants are reminded of the legal considerations governing enablement determinations pertaining to undue experimentation as disclosed in *In re Wands,* 8 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples,

the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer,* 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) Other than β-*gal,* the disclosure fails to provide adequate guidance pertaining to the structural characteristics of any given TAA sequence. The claims are broadly directed toward any TAA sequence insert. In the absence of further direction pertaining to the generic structural requirements for any given heterologous sequence, the skilled artisan could not reasonably predict the nucleotide sequence which would be responsible for suppressive activity.

2) The disclosure fails to identify the molecular determinants modulating the suppressive activity of any given heterologous TAA sequence. As set forth above, the single β-*gal* identified by applicants fails to provide for structural motifs common with other TAA sequences which would function as claimed. Thus, the skilled artisan has only been extended an undue invitation to further experimentation.

3) The disclosure fails to include a clear, concise, and reproducible method for obtaining TAA with the desired activity commensurate in scope with that which is claimed. The disclosure provides a single preparative method wherein β-*gal* is the single expressed tumor antigen determinant contained within the transfected recombinant influenza A virus. However, none of these limitations are present in the claim language. The structural limitations are so vague and indefinite that they fail to provide a reliable and reproducible method for obtaining a functional construct. Applicants are directed toward pages 15-22 of the specification for direction in drafting the process limitations.

4) The prior art is unpredictable and fails to provide any guidance pertaining to the generic structural and functional requirements of the influenza recombinant and influenza recombinant containing vaccine. Additionally, the prior art provides cautionary guidance with respect to specific cell lines employed by applicants in their instant *in vitro* experiments. Thus, conclusions drawn in the specification with respect to *in vitro* experiments are not supported by the art. That is, Rao et al. (J. Immunol. **156**:3357-3365, 1996) when discussing applicants' experimental model teach that "[i]t is important to realize that the tumor model system in which these studies were completed is artificial. β-*gal* represents a large xenogeneic Ag introduced into a tumor cell line and tested in syngenic animals, whereas many of the human TAAs cloned thus far, as well as the mouse Ag PIA, are nonmutated "self" proteins. Thus, the question arises as to whether data derived from the use of such a foreign Ag as a TAA will have relevance to the human situation in which most TAAs appear to be predominantly self Ags. It is worth noting, however, that similar systems, although using foreign proteins as model TAAs, have been instructive, e.g., transfection of the NP gene from vesicular stomatitis virus into EL4 thymoma or transfection of the human carcinoembryonic Ag (CEA) into MC38, a murine adenocarcinoma. Interestingly, the host response to challenge with either CT26.WT or CT25.CL25, expressing β-*gal*, was unaltered, and we found no evidence of systemic immunity elicited to β-*gal*. Both CT26.WT and CT26.CL25 grow equally well and are equally lethal after i.v. injection. Indeed, the β-*gal* model system may be most relevant to human tumors possessing TAAs that originate from viruses, fusion proteins resulting from translocations, or genetic events that result in the expression of foreign proteins arising from mutations, frame-shifts, translation of introns, and the loss of stop codons." It is noted, however, that applicants' disclosure fails to provide any support of influenza A recombinants containing TAAs that originate from viruses, etc.

Restifo (Current Opinion in Immunology, 1996, **8**:658-663) teaches at page 660 that there are concerns with respect to anti-cancer vaccines which are not yet adequately addressed in animal models. "The first concerns the duration of tumors in humans. Whereas tumor deposits may exist for years in humans before they are treated, or even detected, the time course studied in mice is generally measured in weeks and sometimes even in days. The longer kinetics of the tumor-bearing state could increase the heterogeneity of the tumor cells, resulting in cell to cell differences that include antigen expression and antigen processing and presenting efficiency. Human tumor cells can escape immune recognition by a number mechanisms, including loss of β2-microglobulin, downregulation or loss of the expression of particular HLA class I loci, and downregulation, mutation or deletion of the proteasome component molecules latent membrane proteins -2 and -7 as well as of transporters associated with antigen processing. Prior chemotherapy or radiotherapy could complicate problems related to the mutability of tumor cells. Such mutability can result in powerfully resistant tumor cells when the number of tumor cells are counted in trillions. Furthermore, when tumor weight is measured in kilograms rather than in grams or milligrams, issues of peripheral tolerance as well as other forms of specific and nonspecific immunosuppression could be qualitatively different."

5) The breadth of the claimed invention could conceivably encompass an inordinate number of polynucleotides encoding TAAs, most all are inadequately supported by the disclosure as enumerated above.

6) The disclosure fails to meet the legal requirements dictating that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher,* 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). *In re Vaeck,* 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190

U.S.P.Q. 214, 218 (C.C.P.A. 1976). The court stated in *In re Vaeck* that "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of tumor associated antigens, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element."

In summation, the disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating the cancer suppressive activity of any given recombinant influenza virus containing sequence encoding any given TAA, the disclosure fails to provide sufficient guidance pertaining to those variants or derivatives that can reasonably be expected to have and retain suppressive activity. Furthermore, the prior art fails to provide sufficient guidance pertaining to the structural requirements of analogous elements. Thus, the skilled artisan could not possibly predict the nucleotide sequence of various functional equivalents. Accordingly, when all the aforementioned factors are considered together, it would clearly require undue experimentation to practice the claimed invention.

Applicant's arguments with respect to claims 1-11 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laurie Scheiner, whose telephone number is (703) 308-1122. Any inquiry

of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

Laurie Scheiner/LAS
February 21, 2001

LAURIE SCHEINER
PRIMARY EXAMINER